PTO/SB/33 (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
27580-0003001

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
10/084,380-Conf.#3496	02/28/2002

First Named Inventor
Daniel G. Chain

Art Unit	Examiner
1649	Gregory S. Emch

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 46,550

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Mitchell Bernstein/
Signature

Mitchell Bernstein
Typed or printed name

(212) 765-5070
Telephone number

May 12, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

Docket No.: 27580-0003001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Daniel G. Chain

Application No.: 10/084,380 | Confirmation No.: 3496

Filed: February 28, 2002 | Art Unit: 1649

For: SPECIFIC ANTIBODIES TO AMYLOID BETA PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE THEREOF | Examiner: G. S. Emch

SUBMISSION TO ACCOMPANY PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I. INTRODUCTION

This Submission sets forth the basis for Applicant's contemporaneously filed pre-appeal brief request for review of the Final Office Action for the above-identified application that was mailed on November 12, 2009. Applicant has not responded to the aforementioned Final Office Action. Upon entry of an Amendment Under Rule 1.111 that was filed on July 24, 2009, claims 14, 19, 20, 25, 55, 56, 72, 75 and 93-116 are under examination. Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected as allegedly obvious over Becker et al., EP 0613 007 ("Becker") and further in view of Audia et al., U.S. Patent No. 5,965,614. ("Audia"). Claims 14, 19, 20, 25, 72, 75, 99-104 and 109-120 are rejected as obvious over Becker in view of Mak et al., *Brain Res.,* 1994, 19:138-142 ("Mak"). Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 are rejected as obvious over Becker, further in view of Audia as evidenced by Johnson-Wood, et al., *Proc. Natl. Acad. Sci. USA* (1997) ("Johnson-Wood"). The rejection under section 112, second paragraph is the sole remaining rejection in the application.

II. STATEMENT OF APPLICANT'S POSITION

The claims are not obvious over the prior art of record because there is no reasonable expectation of success that Becker could be modified or combined with the secondary references cited by the Examiner to arrive at the claimed invention. Accordingly, the Examiner has not established a *prima facie* case that the claims are obvious over Becker in combination with the secondary references. Additionally, the Examiner has failed to give due consideration to strong objective evidence that at the time the application was filed the claimed invention was not obvious.

Applicant's detailed arguments in support of its position are set out in the response filed July 24, 2009, which is incorporated herein by reference. Many points raised by the Examiner in the Final Office were not raised in the previous Office Action that was mailed on May 27, 2009 and therefore were not addressed in the aforementioned response. Applicant addresses these newly raised points here.

III. THE EXAMINER FAILS TO PROVIDE A VALID RATIONALE TO CONCLUDE THAT ANTIBODIES THAT RECOGNIZE A-BETA IN AN ALPHA-HELICAL CONFORMATION WOULD BE EFFECTIVE IN INHIBITING A-BETA NEUROTOXICITY

Applicant's previous response detailed how Becker and Soto represent the state of the art when the application was filed, which held that the pathogenic agent in Alzheimer's disease was neuritic plaques containing insoluble, deposited A-beta. The Examiner, however, continues to rely on a selective and, in some instances, a mistaken, reading of Becker to support his mistaken position that Becker teaches antibodies that recognize A-beta in the alpha-helical conformation would be useful as therapeutics.

Thus, when measured against the full content of Becker, the Examiner overreaches in stating on page 8 of the Final Office Action that antibodies to A-beta in the alpha-helical conformation "are used in therapeutics." Becker says generally that, "The antibodies of the present invention are especially preferred in the diagnosis and/or treatment of Alzheimer's disease." Upon considering Becker as a whole, one of ordinary skill in the art would clearly recognize that antibodies specific for A-beta in the alpha helical conformation might be useful in diagnostic methods that compare the amount of A-beta in the helical conformation to the amount of A-beta in the β-sheet conformation and further might be useful in assays that identify compounds that are useful in inhibiting neurotoxicity of A-beta. These uses, however, do not equate with the suggestion

that antibodies specific for alpha helical A-beta are useful for treating Alzheimer's disease or inhibiting the neurotoxicity of A-beta.

The Examiner attempts to circumvent Becker's lack of a suggestion to use antibodies specific for alpha helical A-beta as therapeutics by stating on page 9 of the Final Office Action that "it would at least be obvious for the artisan of ordinary skill to try using antibodies to the alpha helix or random coil conformation for treatment." An "obvious to try" rationale, however, requires a reasonable expectation of success, which is clearly lacking here. Becker teaches that it is A-beta in the β-sheet conformation that is the pathogenic agent in Alzheimer's disease. Becker makes no connection between alpha helical-A beta and Alzheimer's disease or A-beta-related neurotoxicity. There is thus no logical rationale to conclude that antibodies to A-beta in the alpha helical or random coil conformation would have any therapeutic value.

The Examiner's discussion of the assays set out in claims 3 and 5 of Becker perpetuates the mischaracterization that antibodies to A-beta in the alpha helical or random coil are useful as therapeutics. Claims 3 and 5 are directed to assays for identifying compounds that reduce neurotoxicity caused by A-beta that has assumed a β-sheet conformation. Becker makes no suggestion to test antibodies that are specific for the A-beta in the alpha helical or random coil conformation in such an assay, notwithstanding that Becker specifically discloses such antibodies and discusses them at length.

Undeterred by Becker's failure to suggest that antibodies that are specific for A-beta in the alpha helical or random coil conformation should be used in an assay of A-beta neurotoxicity, on page 12 of the Final Office Action the Examiner pieces together an illogical rationale for doing so from disparate parts of Becker. The Examiner thus cites Becker for the proposition that, "The use, therefore, of β-amyloid peptide that has adopted a predominantly β-sheet conformation allows the development of compounds that specifically inhibit the neurotoxicity." This statement is consistent with the art-accepted finding that the β-sheet conformation of A beta is neurotoxic. It follows logically that incubating A-beta having a β-sheet conformation with compounds provides an assaying for compounds that inhibit A-beta neurotoxicity. It does not logically follow, however, that a discussion of conformation-specific antibodies in a separate paragraph would lead one of ordinary skill in the art to conclude that antibodies specific for the alpha helical conformation of A beta are potential inhibitors of A beta-related neurotoxicity. To the contrary, it is logical to

conclude that antibodies that fail to bind A-beta in the β-sheet conformation would not be useful in inhibiting the neurotoxicity of A-beta that was already predominantly in the β-sheet conformation.

The Examiner, however, apparently assumes the placement of paragraphs to be determinative in reaching the conclusion that antibodies specific for the alpha helical conformation of A-beta are potential inhibitors of A-beta-related neurotoxicity. The paragraph cited by the Examiner on page 12 of the Final Office Action begins, however, "Another embodiment of this invention encompasses conformationally-specific antibodies and antibody fragments which bind to β-amyloid peptides in a secondary structure-specific manner." Emphasis added. The characterization of conformation-specific antibodies as "another embodiment" of the invention clearly belies the Examiner's assertion that the juxtaposition of a paragraph concerning an assay for inhibiting the neurotoxicity of A-beta in the β-sheet conformation with a paragraph discussing conformation-specific antibodies leads to a conclusion that antibodies recognizing the alpha helicial conformation of A-beta are potential inhibitors of A-beta-related neurotoxicity.

Additionally, Becker fails to provide any support for the Examiner's statement on page 12 of the Final Office Action that, "If the artisan then tested these antibodies in the claimed assay, the artisan would necessarily see that antibodies to the α-helix conformation would prevent neurotoxicity since the β-amyloid peptides would be prevented from forming the neurotoxic β-sheet conformation." As discussed above, Becker assays the ability of compounds to inhibit the neurotoxicity of A beta that has already "adopted a predominantly β-sheet conformation." *See* Final Office Action at page 12. It is irrational to assert that antibodies that prevent A-beta from assuming the β-sheet conformation would have an effect on neurotoxicity due to the β-sheet A-beta conformer that has already formed. Moreover, the Examiner fails to provide any support for his presumption that the binding of antibodies to the alpha helical conformation of A-beta would prevent A-beta from converting to the β-sheet conformation. The Examiner thus again overreaches to find a reason to modify Becker to arrive at the instant claims.

In short, as set forth in Applicant's previous response, none of Becker, the secondary references, nor any other rationale offered by the Examiner provides a basis for combining the prior art of record to arrive at the instant claims. The claims are thus not obviousness, as set out by the Examiner.

IV. THE EXAMINER'S CONSIDERATION OF APPLICANT'S DECLARATION IS FLAWED

The Examiner failed to give proper consideration to Daniel Chain's Declaration Under 37 CFR 1.132. First, the Examiner's statement on 24 of the Final Office Action that, "As set forth above, the teachings of Becker, Audia and Mak provide the expectation that 3D6 and antibodies to Aβ34-40 would be effective in treating Alzheimer's disease," effectively requires the claimed invention to show unexpected results against itself. Unexpected results, however, are measured against the closest prior art. Additionally, the Examiner's assertion that the unexpected results provided in the Chain Declaration are not commensurate in scope with the claims is not believed to be well taken. The bapineuzumab and PF-04360365 antibodies are free-end specific antibodies that bind respectively to epitopes comprising a free-amino terminus at position 1 of A beta and a free C-terminus at position 40 of A beta, as called for in the claims. The Examiner has failed to provide any rationale as to why bapineuzumab and PF-04360365 are not representative of all free-end specific antibodies that bind the free amino terminus at position 1 of A beta or the free C-terminus at position 40 of A beta.

The Examiner thus erred by failing to give proper consideration to the Chain Declaration.

V. CONCLUSION

For the reasons set out above and in Applicant's response filed July 24, 2009, all rejections under 35 U.S.C. §103 should be withdrawn.

Dated: May 12, 2010

Respectfully submitted,

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